Graphical presentation of systematic review of the epidemiology literature on formaldehyde and lymphohematopoietic cancers.

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Abstract

Background: EPA's IRIS program is currently developing a Toxicological Review of Formaldehyde. As part of the comprehensive evaluation of potential hazards associated with exposure to formaldehyde, the literature related to lymphohematopoietic cancers is being evaluated. There are multiple meta-analyses available that have evaluated potential associations. However, EPA is conducting an independent systematic review of the entire body of literature.

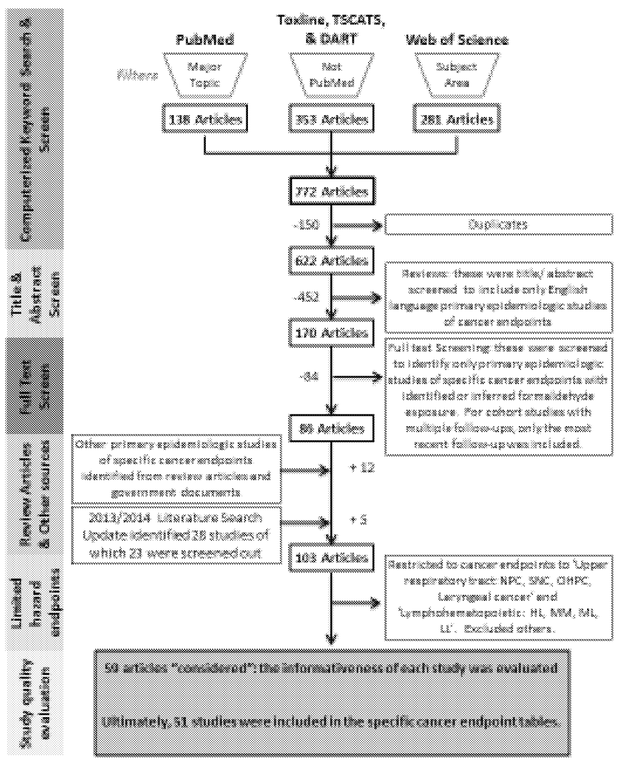
Aims: To provide a systematic graphical illustration of the results of the epidemiologic literature describing potential associations with formaldehyde exposures and the occurrence of lymphohematopoietic cancers.

Methods: We searched the epidemiologic literature on lymphohematopoietic cancer subtypes potentially related to formaldhyde exposure, and reviewed more than 150 studies. EPA prepared figures detailing the literature search process and summarized the relevant evidence in tables and enriched multidimensional forest plots for four specific lymphohematopoietic cancers including Hodgkin lymphoma, multiple myeloma, lymphatic leukemia and myeloid leukemia.

Results: The literature search identified more than 25 relevant epidemiologic studies indicating the presence or absence of associations between formaldehyde exposure and the occurrence of lymphohematopoietic cancers subtypes. Forest plots with extensive annotation were used to depict the results graphically.

Conclusions: There is a substantial body of epidemiologic literature to evaluate the potential association between formaldehyde exposures and certain subtypes of lymphohematopoietic cancer. Detailed graphical presentation of study results can aid in evaluating consistency of effects by grouping study results by differences in study designs, populations, and exposure ranges among other factors.

Flow chart of literature search results conducted for Toxicological Review



Overview

- Graphical displays of epidemiologic results are, in general, limited to the effect estimate that is the lowest common denominator among a set of studies.
- For example, a common scenario involves the display of results from multiple studies, some with just a single measure of effect like a standardized mortality ratio (SMR), while others report an SMR as well additional effect estimates by categories of ordinal exposure groups based on higher quality individual-level exposure data.
- In some graphical presentations, the more detailed results based on higher quality exposure information are not presented so as to maintain the comparability of effect estimates.
- The following are examples of a more systematic approach to graphical presentations that display substantially more information.
- These graphs are annotated to included multiple dimensions of information:
  - Effect metric (SMR, PMR, SPIR, OR, RR)
  - Effect size
  - Confidence intervals
  - Number of cases
  - Methods of exposure assessment
  - Exposure category within a study
  - Exposure range
  - Multiple results per study
  - Industry type
- Annotated forest plots offer an enhanced platform to convey the rich multivariate details of systematic reviews and can allow the investigator to understand and explain the results with far greater clarity.

All Studies Reporting Myeloid Leukemia Risk Estimates

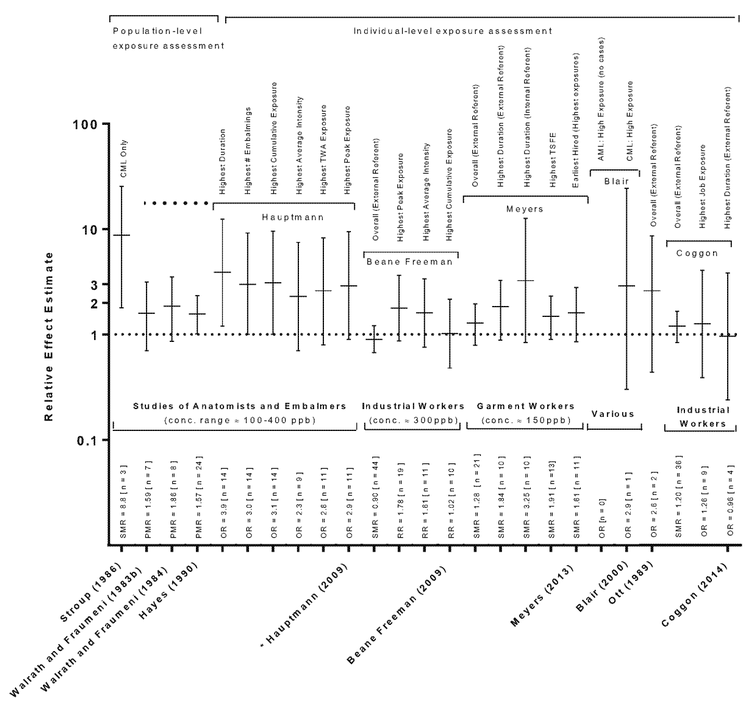


Figure ML. Epidemiologic studies reporting myeloid leukemia risk estimates. Results specifically for acute myeloid leukemia (AML) or chronic myeloid leukemia (CML) are noted by these abbreviations. SMR: standardized mortality ratio. PMR: proportionate mortality ratio. RR: relative risk. OR: odds ratio. For each measure of association, the number of exposed cases is provided in brackets (i.e., [n=3]). For studies reporting results on multiple metrics of exposure, each metric is included; however, only the highest category of each exposure metric is presented in the figure. * The dotted line extending from Hauptmann (2009) reflects that study's inclusion of the original cohorts from Walrath and Fraumeni (1983b, 1984) and Hayes et al. (1990), which were combined with extended follow-up in Hauptmann et al. (2009) in a nested case-control study with internal referents.

All Studies Reporting Lymphatic Leukemia Risk Estimates

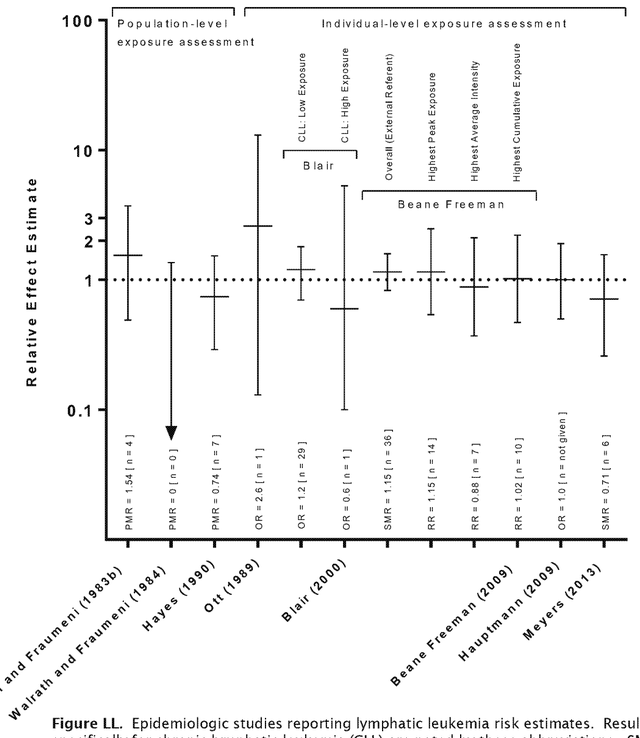


Figure LL. Epidemiologic studies reporting lymphatic leukemia risk estimates. Results specifically for chronic lymphatic leukemia (CLL) are noted by these abbreviations. SMR: standardized mortality ratio. PMR: proportionate mortality ratio. RR: relative risk. OR: odds ratio. For each measure of association, the number of exposed cases is provided in brackets (i.e., [n=4]). For studies reporting results on multiple metrics of exposure, each metric is included; however, only the highest category of each exposure metric is presented in the figure.

All Studies Reporting Multiple Myeloma Risk Estimates

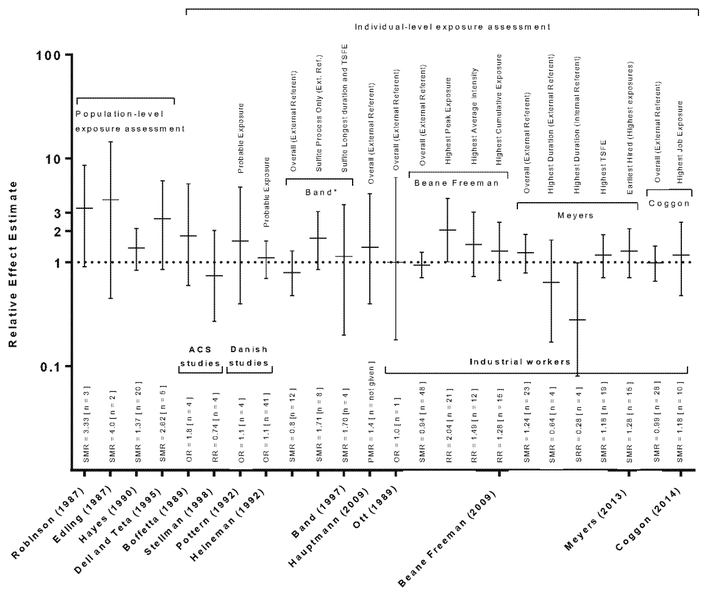


Figure MM. Epidemiologic studies reporting multiple myeloma risk estimates. SMR: standardized mortality ratio. PMR: proportionate mortality ratio. RR: relative risk. OR: odds ratio. For each measure of association, the number of exposed cases is provided in brackets (i.e., [n=3]). For studies reporting results on multiple metrics of exposure, each metric is included; however, only the highest category of each exposure metric is presented in the figure. * Note that the confidence intervals for Band et al. (1997) are 90% rather than 95%.

All Studies Reporting Hodgkin Lymphoma Risk Estimates

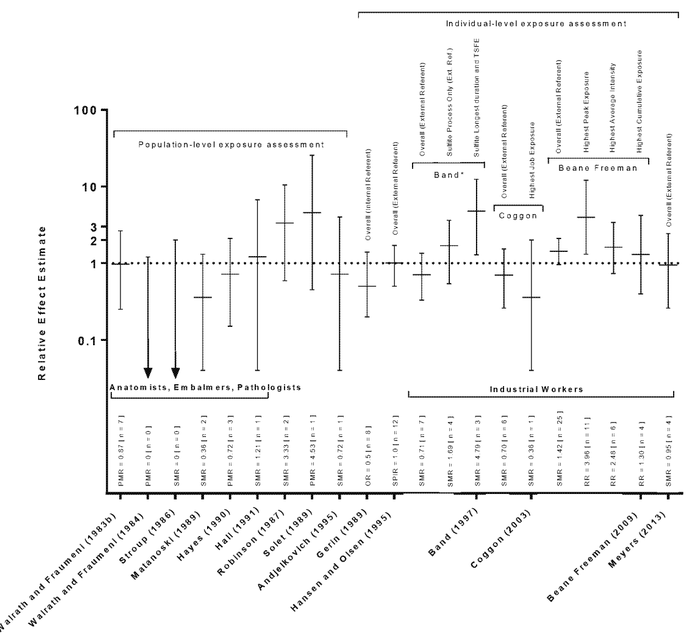


Figure HL. Epidemiologic studies reporting multiple Hodgkin lymphoma estimates. SMR: standardized mortality ratio. PMR: proportionate mortality ratio. RR: relative risk. OR: odds ratio. For each measure of association, the number of exposed cases is provided in brackets (i.e., [n=7]). For studies reporting results on multiple metrics of exposure, each metric is included; however, only the highest category of each exposure metric is presented in the figure. * Note that the confidence intervals for Band et al. (1997) are 90% rather than 95%.